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10/539,289	06/16/2005	Gera Neufeld	29432	5166

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,289	NEUFELD, GERA	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *4-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-23 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-3, in the reply filed on 10/25/07 is acknowledged. Applicant does not indicate whether the election is with or without traverse, but because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3 are under consideration.

Specification

The disclosure is objected to because of the following informalities:

(1) In the Brief Description of the Drawings (pg 4-5), the description of Figure 1 incorrectly refers to Figure 2a instead of Figure 1a. Specifically, line 1 of page 5 states, "...Figure 2b = variant VEGF145 cDNA (SEQ ID NO: 2)..." However, Figure 2b shows an amino acid sequence (SEQ ID NO: 4) whereas Figure 1a shows SEQ ID NO: 2. This objection would be rendered moot if the specification, for example, were amended to recite "...Figure 1a = variant VEGF145 cDNA (SEQ ID NO: 2)" on line 1 of page 5.

(2) On page 6, line 18 the word "weak" is misspelled as "week" (i.e., "...exhibits relatively week binding...").

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the metes and bounds of the claimed polypeptide are unclear. The claim recites that the polypeptide is "devoid of a VEGFR-1 binding activity". The term "devoid" suggests a complete absence. However, the exemplary polypeptide disclosed in the specification retains a degree of VEGFR-1 binding activity even if it is 1900-fold less than the wild type protein (pg 25, lines 21-25). As such, the phrase "devoid of a VEGFR-1 binding activity" has been interpreted to encompass any polypeptide that has less than full VEGFR-1 binding activity (i.e., is devoid of some degree of binding).

Claim 2 is indefinite because it is unclear what is meant by "said polypeptide is set forth by SEQ ID NO: 4". The specification does not provide a limiting definition of "set forth by". As such, it is unclear whether or not the claim encompasses variants of SEQ ID NO: 4. If Applicant wishes to claim only the polypeptide of SEQ ID NO: 4, the claim could be rendered definite by amending the claim, for example, to recite "said polypeptide consists of the amino acid sequence of SEQ ID NO: 4".

Claim 3 is rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide of SEQ ID NO: 4, does not

reasonably provide enablement for an isolated VEGF145 polypeptide devoid of a VEGFR-1 binding activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is directed to isolated $VEGF_{145}$ polypeptides. The prior art teaches that $VEGF_{145}$ is a splice variant of human VEGF containing exons 1-6 and 8 (see Abstract of Poltorak et al, 1997; cited previously). Poltorak further teaches that $VEGF_{145}$ is just one of several VEGF isoforms:

> "The human VEGF isoforms are generated by alternative splicing from a single gene ... The domain encoded by exons 1-5 contains information required for the recognition of the known VEGF receptors KDR/*flk-1* [aka VEGFR-2] and *flt-1* [aka VEGFR-1]... and is present in all VEGF isoforms. The amino acids encoded by exon 8 are also present in all the VEGF splice variants. The VEGF isoforms are distinguished by the presence or the absence of the peptides encoded by exons 6 and 7 of the VEGF gene. VEGF121 is 121 amino acids long and lacks both exons. VEGF165 contains the exon 7-encoded peptide, whereas VEGF189 contains both 6 – and exon 7-encoded peptides" (pg 7151).

The breadth of the claims is as follows. Independent claim 1 encompasses any "$VEGF_{145}$ devoid of a VEGFR-1 binding activity". Claims 2 and 3 each depend from claim 1 and limit the polypeptide to one "set forth by SEQ ID NO: 4" (claim 2) or "capable of binding to VEGFR-2" (claim 3). As set forth in the section Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the phrase "devoid of a VEGFR-1 binding activity" is not defined in the specification and is indefinite in view of the teachings in the specification (pg 25) that indicate that the mutations that produce "1900 fold less

affinity" will produce VEGF variants that meet the limitations of the claims. As such, the phrase "devoid of a VEGFR-1 binding activity" has been interpreted to encompass any polypeptide that has less than full VEGFR-1 binding activity (i.e., is devoid of some degree of binding). Claim 2 is also indefinite because it is unclear what is meant by "said polypeptide is set forth by SEQ ID NO: 4" and has been interpreted to encompass variants of SEQ ID NO: 4 with one or more mutations.

The specification provides examples of polypeptides that are encompassed by the term "$VEGF_{145}$", but does not provide a limiting definition of the term. The specification teaches that "the term $VEGF_{145}$ polypeptide refers to the vascular endothelial growth factor isoform 145 ($VEGF_{145}$) protein such as the human $VEGF_{145}$ (GenBank Accession Number: NP_003367) which is set forth by SEQ ID NO: 3. The $VEGF_{145}$ polypeptide can be encoded by a naturally occurring or synthetic polynucleotide. According to preferred embodiments used by the present invention the polynucleotide used is at least 90 %, at least 95%, more preferably, at least 98 % homologous to the polynucleotide sequence set forth by SEQ ID NO: 1" (pg 6-7). The specification further provides examples of mutated polypeptides that are "at least 75 %" homologous to SEQ ID NO: 3 ("wild type" $VEGF_{145}$). While the specification provides examples of broad genus of $VEGF_{145}$ variants, the specification places no limit on the number of mutations that can be found in a "$VEGF_{145}$" polypeptide.

The specification provides the following working example related to the claimed invention. Example 1 (pg 24-26) describes "construction of a $VEGF_{145}$ variant that lacks VEGFR-1 binding ability". The specification teaches, "To generate a $VEGF_{145}$ variant form that lacks the VEGFR-1 binding capacity, the cDNA coding the $VEGF_{145}$ form was subjected to the following site directed mutagenesis: Asp63Ser, Gly65Met and Leu66Arg" (pg 25). There are no working examples where the binding to a receptor is actually measured. Instead, the specification teaches, "Similar mutations ... which introduced in the form resulted in a variant which binds to $VEGF_{145}$ with normal affinity, however with 1900 fold less affinity to VEGFR-1 receptor" and cites (Li et al, 2000; cited

previously). Therefore, the specification provides a single putative working example of the vast genus of $VEGF_{145}$ mutants encompassed by the claims.

The prior art provides some guidance as to mutations to make variant VEGF polypeptides that bind VEGFR-2 (KDR) but have reduced binding affinity for VEGFR-1 (Flt-1); specifically, see Li et al, 2000 and Cunningham et al, WO 00/63380 (cited below). However, the scope of the variants encompassed by the instant claims goes far beyond the limited mutations taught by Cunningham and Li. The scope of "devoid of a VEGFR-1 binding activity" has been interpreted to encompass any reduction of VEGFR-1 binding activity. However, the scope of this claim also encompasses mutants that are completely devoid of VEGFR-1 binding activity. Neither the specification or the prior art teaches a VEGF mutant that is completely devoid of VEGFR-1 binding activity and that retains VEGFR-2 binding activity. As to the unpredictability of predicting other combinations of mutations that will work in the claimed invention, Li teaches, "...we combined the mutations from both KDR-selective variants ... the resulting variant with seven mutations was nearly inactive in cell-based assays and had considerably reduced (more than 200-fold) KDR binding affinity..." (pg 29828).

Applicant does not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of polypeptides of SEQ ID NO: 4. The specification has not provided a working example of the use of any variant of the polypeptide of SEQ ID NO: 4, nor sufficient guidance so as to enable one of skill in the art to make such a usable variant. The specification has failed to teach which amino acids of SEQ ID NO: 4 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 4 and yet still retain a characteristic of the parent polypeptide, e.g., the ability to bind VEGFR-2 (KDR). Furthermore, claims 1 and 2 broadly encompass variants that lack the essential function required to use the polypeptides (i.e., being "capable of binding to VEGFR-2"). Applicant has not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure or function, between the protein corresponding to SEQ ID NO: 4 and variants of said protein. If a variant of the protein is

to have a structure and function similar to SEQ ID NO: 4, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein. Conversely, if a protein variant of SEQ ID NO: 4 need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells, (1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" (pg 492-495)]. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues;

therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand

what Applicant is claiming and what Applicant has possession of. Claims 1-3 are genus claims because the claims are directed to variant polypeptides. Each genus is highly variant because a significant number of structural differences between genus members are permitted. The claims only require the claimed polypeptides share some structural similarity to $VEGF_{145}$. Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity. However, the instant specification fails to describe the entire genus of polypeptides that are encompassed by each of these claims. From the specification, it is clear that Applicant has possession of an isolated polypeptide of SEQ ID NO: 4. The specification fails to describe or teach any other polypeptide which differs from the sequence of SEQ ID NO: 4 and retains the recited characteristic of "devoid of a VEGFR-1 binding activity" and the necessary functional activity of "capable of binding to VEGFR-2". The claims, however, are not limited to a polypeptide of SEQ ID NO: 4.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative

teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polypeptides of SEQ ID NO: 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al, 2000 (Journal of Biological Chemistry. 275(38): 29823-29828; cited previously).

Li teaches a VEGF polypeptide that has reduced binding to Flt1 (VEGFR-1) due to single mutation of residue 63 or 66, but that retains binding to KDR (VEGFR-2) that is equivalent to the non-mutated form (see Table I on page 29825). These polypeptides consists of residues 1-109 of VEGF with either of the indicated mutations at residue 63 or 65. Li further teaches another variant with a triple mutation of "Asp-63 to Ser, Gly-65 to Met, and Leu-66 to Arg ("KDR-sel2") (pg 29826); these variant had "approximately wild-type binding affinity for KDR [VEGFR-2]... but bound ... 1900-fold more weakly to ... Flt-1 [VEGFR-1]" (pg 29827). As compared with the "wild type" $VEGF_{145}$ isoform, each of these proteins include a truncation of residues 110-145. The specification teaches that "$VEGF_{145}$" proteins of the invention include those with mutations, but does not place any limitation on the number of mutations present. As such, the instant claims encompass a $VEGF_{145}$ polypeptide variants with multiple mutations, such as a mutation of residue 63, 65 and/or 66 and deletion of residues 110-145. Furthermore, as set forth in the section, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph" the term "devoid of a VEGFR-1 binding activity" is indefinite in view of the teachings of the specification and has been interpreted broadly to encompass any polypeptide that has less than full VEGFR-1 binding activity (i.e., is devoid of some degree of binding). As such, the polypeptides taught by Li et al anticipate claims 1 and 3.

Claim 2 is also included in this rejection for the following reasons. As set forth in the section, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph" the term "as set forth by

SEQ ID NO: 4" is indefinite and has been broadly interpreted to encompass variants of SEQ ID NO: 4 with one or more mutations. As such, the polypeptides taught by Li et al anticipate claim 2.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Cunningham et al, WO 00/63380 (published 10/26/00).

Cunningham teaches a mutant $VEGF_{109}$ polypeptide ("LK-VRB-2s") and a mutant $VEGF_{165}$ sequence ("LK-VRB-2f"), each with three point mutations: Arg-63-Ser; Gly-64-Met; and Leu-66-Arg (see pg 30, line 26 through pg 31, line 5 and Table 2). Table 6 (pg 37) shows these two variants can each bind the KDR receptor but have greatly reduced FLT-1 [VEGFR-1] binding activity. For the reasons described above, these mutant VEGF polypeptides anticipate instant claims 1-3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al, WO 00/63380 (published 10/26/00; cited above) in view of Poltorak et al, 1997 (Journal of Biological Chemistry. 272(11): 7151-7158; cited previously).

It is noted that this rejection pertains to a specific embodiment encompassed by claims 1-3; specifically, an isolated $VEGF_{145}$ polypeptide with the amino acid sequence of SEQ ID NO: 4. The instant specification teaches that SEQ ID NO: 4 has three point mutations (Arg-63-Ser; Gly-64-Met; and Leu-66-Arg) as compared with the "wildtype" $VEGF_{145}$ sequence (SEQ ID NO: 3).

The teachings of Cunningham are described above. Cunningham further teaches that the term "VEGF" as used therein refers to the "the 165- amino acid vascular

endothelial growth factor and related 121-, 189- and 206- amino acid vascular endothelial cell growth factors... together with the naturally occurring allelic and processed forms thereof" (pg 8, line 6-11) and to "to truncated forms of the polypeptide comprising amino acids 8 to 109 or 1 to 109 of the 165-amino acid vascular endothelial growth factor" (pg 8, lines 12-14). Cunningham further teaches that "[p]referred VEGF variants have one or more amino acid substitutions at positions 63, 65 and/or 66 of VEGF, wherein the amino acid residue at position 63 is substituted with serine, the amino acid residue glycine at position 65 is substituted with methionine, and/or the amino acid residue leucine at position 66 is substituted with arginine" (pg 4, line 43 to pg 5, line 4). Cunningham further teaches that VEGF variants include those with amino acid deletions (pg 11, line 36) and that such deletions "generally range from about 1 to 30 residues, more preferably 1 to 10 residues, and typically are contiguous" (pg 12, lines 19-20). Cunningham further teaches that "Preferred VEGF variants of the invention will additionally or alternatively induce endothelial cell proliferation (which can be determined by known art methods such as the HUVEC proliferation assay in the Examples)" (pg 14, lines 1-4). Cunningham does not teach a wildtype or mutated VEGF sequence with 145 amino acids.

Poltorak teaches that $VEGF_{145}$ is one of several splice variants of VEGF, including others that consist of 121, 165 and 189. Poltorak teaches that the 145 amino acid form lacks exon 6 (as opposed to the 165 form which lacks exon 7), but "the domain encoded by exons 1-5 contains information required for the recognition of the known VEGF receptors KDR/*flk-1* [aka VEGFR-2] and *flt-1* [aka VEGFR-1]... and is present in all VEGF isoforms" (pg 7151). Poltorak further teaches that "$VEGF_{145}$ was found to induce endothelial cell proliferation and in vivo angiogenesis, in agreement with previous studies that have indicated that these functions are not dependent on the presence of either exon 6 or exon 7" (pg 7156).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make the amino acid sequence of SEQ ID NO: 4 by making the mutations taught by Cunningham (to residues 63, 65 and 66) in the $VEGF_{145}$ sequence

taught by Poltorak. The person of ordinary skill in the art would be motivated to do so because (1) $VEGF_{145}$ meets the definitions of a "processed" or "deleted" VEGF variant as suggested for use by Cunningham as part of the KDR-selective VEGF of the invention and (2) in the absence of other evidence, the mutated $VEGF_{145}$ sequence could used for endothelial cell proliferation as well as the mutated $VEGF_{165}$ taught by Cunningham. Further, a person of ordinary skill in the art would have had a reasonable expectation of success because producing mutated proteins is routine in the art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646